Structure and Reactivity of Dinuclear Cobalt(III) Complexes with Peroxide and Phosphate Diester Analogues Bridging the Metal Ions

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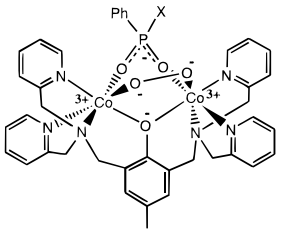
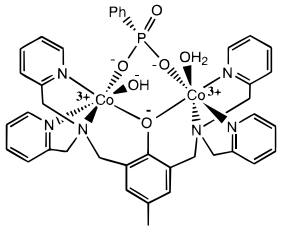
There is much current interest both in chemistry[1] and in biology[2] in understanding how two metal ions cooperatively hydrolyze phosphate esters. Metal ion-catalyzed hydrolysis of phosphate diesters with poor leaving groups is of particular interest since some of the most important molecules of life (DNA, RNA, phospholipids) contain such linkages. Hydrolyzing phosphate diesters with poor leaving groups is an elusive goal as they are enormously more stable compared to phosphate diesters with good leaving groups.[3,4] It has been suggested that metal-bound peroxides can be effective nucleophiles for cleaving amides[5] and phosphates.[6] Here we examine the conversion of **1a** to **2**. The



1a: X = -OMe
1b: X = -Ph



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structure of **1b** was determined in this study as a model for the structure of **1a** while the structure of **2** was determined previously.[7]

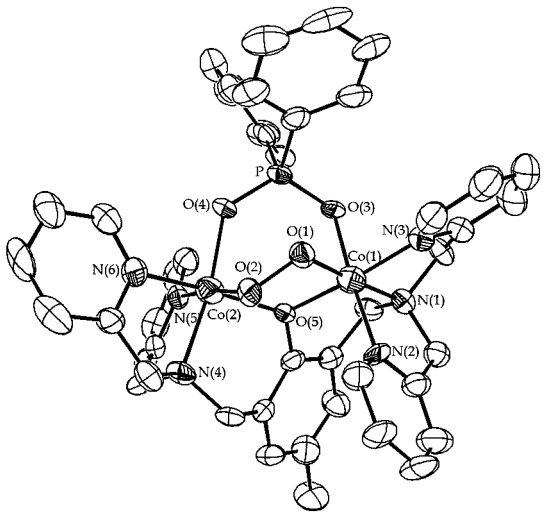

Figure 1. X-ray structure of **1b** (ORTEP representation; ellipsoids at 50% probability level). Selected distances (Å) and angles (deg): Co1−Co2 3.2319(25), Co1−N1 2.024(7), Co1−N2 1.924(7), Co1−N3 1.918-(7), Co1−O1 1.863(6), Co1−O3 1.946(5), Co1−O5 1.915(6), Co2−N4 1.979(4), Co2−N5 2.017(7), Co2−N6 1.934(7), Co2−O2 1.862(6), Co2−O4 1.928(5), Co2−O5 1.947(6), O1−O2 1.410(8); O3−P−O4 116.9-(3), Co1−O3−P 119.7(3), Co2−O4−P 132.2(4), O1−Co1−O3 90.28-(25), N1−Co1−N2 85.7(3), O2−Co2−O4 93.1(3), N4−Co2−N5 83.8(3).

Complex **1b** was prepared by the same method used for making **2**.[7] The ^{31}P NMR spectrum of the dinuclear Co(III) complex shows a sharp singlet (**1b**: DMSO (trimethyl phosphate) δ 51 ppm) indicating that there is only one diastereomer in the sample. The structure of **1b** (Figure 1) closely resembles that of **2** except that the bridging peroxide in **1b** is replaced with solvent molecules in **2**.[8] It appears that when phosphate monoester analogues are used instead of phosphate diester analogues in the synthesis of the dinuclear Co(III) complex, the bridging peroxide is more readily exchanged with solvent water molecules. Replacing diphenyl phosphinate in the above synthesis with methyl phenylphosphonate gave **1a**.[9] Unfortunately, we were unable to prepare the corresponding dinuclear Co(III) complex with a bridging phosphate diester by the same synthetic procedure. However, phosphonate monoesters are excellent models of phosphate diesters in that they have comparable reactivities as discussed below. Unlike in **1b**, the phosphorus center in **1a** is chiral and two ^{31}P NMR signals are observed for the two diastereomers (**1a**: DMSO (trimethyl phosphate) δ 43 and 40 ppm in a ratio of ∼3:1).

Hydrolysis of the phosphonate ester bond in **1a** was monitored by ^{1}H and ^{31}P NMR. In a typical kinetic experiment, **1a** was dissolved in DMSO-d_6 (2 mM) and the hydrolysis reaction was started by adding 0.5 equiv volume of a buffered solution of D_2O (10 mM *N*-ethylmorpholine, pD 7, 25 °C). Production of methanol from the hydrolysis of **1a** was monitored by ^{1}H NMR. The ^{1}H NMR of the product of hydrolysis of **1a** matches that of a genuine sample of **2** synthesized from phenylphosphonate. Conversion of **1a** to **2** was also monitored by ^{31}P NMR (Figure S1).

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(8) Crystal structural data for **1b**$(ClO_4)_2$: $Co_2C_{45}H_{43}N_6O_{13}PCl_2$, monoclinic, space group *P*21/*n*, a = 11.6526(11) Å, b = 11.1944(9) Å, c = 36.026(3) Å, b = 94.449(7)°, V = 4685.2(7) Å^3, Z = 4; 5886 measured reflections, 3411 with $I > 2.5s(I)$, 623 parameters, R = 0.062 and R_w = 0.062, GOF = 1.66. Anal. Calcd for $C_{45}H_{43}N_6O_{13}PCl_2Co_2$ (**1b**·$(ClO_4)_2$): C, 49.33; H, 3.96; N, 7.67; Cl, 6.47; Co, 11.76. Found: C, 49.49; H, 4.20; N, 7.93; Cl, 6.35; Co, 10.71.

(9) Anal. Calcd for $C_{40}H_{41}N_6O_{14}PCl_2Co_2$ (**1a**·$(ClO_4)_2$): C, 45.78; H, 3.94; N, 8.01; Cl, 6.76; Co, 11.23. Found: C, 45.30; H, 3.98; N, 7.90; Cl, 7.01; Co, 10.94.

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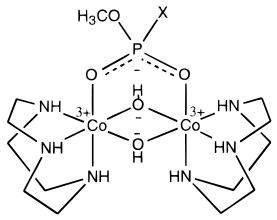
The pseudo-first-order rate constant for the hydrolysis of the ester bond in **1a** is 5×10^{-7} s^{-1} under the above experimental conditions. This represents a substantial rate acceleration for the hydrolysis of the metal-coordinated phosphonate ester over that of the metal-free substrate. In general, phosphonate monoesters are about as stable as phosphate diesters. The second-order rate contant for hydroxide-catalyzed hydrolysis of bis(*p*-nitrophenyl) phosphate,[3] *p*-nitrophenyl phenylphosphonate,[10] and *p*-nitrophenyl methyl phosphonate[11] at 25 °C are 2.0×10^{-5}, 8.3×10^{-5}, and 2.8×10^{-5} M^{-1} s^{-1}, respectively.[12] Assuming that the second-order rate constant for hydroxide-catalyzed hydrolysis of methyl phenyl phosphonate is comparable to that for the hydrolysis of dimethyl phosphate (6.8×10^{-12} M^{-1} s^{-1}),[4] the pseudo-first-order rate constant for hydroxide-catalyzed hydrolysis of the monoester at pH 7 should be $\sim 10^{-18}$ s^{-1}. This gives a crude estimate for the rate acceleration of $\sim 10^{11}-10^{12}$-fold.

It is interesting to compare the reactivity of the dinuclear complex to that of previously reported mononuclear metal complexes. Mononuclear Co(III) complexes provide $\sim 10^7$-fold rate acceleration for hydrolyzing phosphate diesters[4,13] when the N−Co−N bond angle opposite the O−Co−O bond angle is locked into a five-membered ring as it is in our dinuclear system (**1b**). Hence, there appears to be considerable gain in reactivity on going from the mononuclear to the dinuclear complex.

There are two reasonable mechanisms for the cleavage of the phosphonate ester bond in **1a**. The bridging peroxide may act as an intramolecular nucleophilic catalyst[14] or it may first be replaced by solvent molecules followed by intramolecular nucleophilic attack of the bridging phosphonate by the metal hydroxide. Metal-bound peroxides have been implicated in the cleavage of amides[5] and phosphates.[6] To distinguish the mechanistic possibilities, ^{18}O labeling experiments were performed. The incorporation of ^{18}O into the product phosphonate **2** can be detected by ^{31}P NMR spectroscopy since it results in an upfield shift of the phosphonate signal by ~0.02 ppm.[15] When **1a** was allowed to react with 50% ^{18}O-labeled D_2O, the product phosphonate peak appeared as a doublet, clearly demonstrating the incorporation of O-18 from the solvent to the product (Figure S2). In contrast, if **1a** is first synthesized with 50% ^{18}O-labeled O_2 and then hydrolyzed with unlabeled D_2O, there is no incorporation of O-18 into the product.[16] We therefore conclude that the cleavage of the phosphonate ester in **1a** takes place by intramolecular nucleophilic attack of metal hydroxide on the bridging phosphonate ester. The bridging peroxide in **1a** may still be involved in cleaving phosphonate esters with good leaving groups. Consistent with this interpretation, we were unable to synthesize the dinuclear Co(III) complex with *p*-nitrophenyl phenylphosphonate bridging the two metal centers because *p*-nitrophenol is released during the synthesis.

We recently reported that phenyl phosphate coordinated to the dinuclear metal complex in **2** is hydrolyzed $\sim 10^{11}$ times more rapidly than uncoordinated phenyl phosphate.[7] While metal-promoted hydrolysis of activated phosphates with good leaving groups is quite common, hydrolyzing unactivated phosphate diesters with poor leaving groups remains a major challenge. Attempt at hydrolysis of dimethyl phosphate coordinated to a mononuclear Co(III) complex resulted in simple dissociation of the diester.[17] In another recent study,[18] it was shown that the phosphate diester bond in **3a** with a good leaving group is hydrolyzed $\sim 10^{11}$ times more rapidly than the metal-free diester while the phosphate diester in **3b** with poor leaving groups



3a: X = -OPhNO$_2$
3b: X = -OMe

dissociates from the dinuclear Co(III) complex without any observable hydrolysis of the diester bond.[19] Hence, a catalyst that provides large rate acceleration for hydrolyzing activated phosphates do not necessarily provide comparable rate acceleration for hydrolyzing unactivated phosphates. In sharp contrast to the result for **3b**, **1a** is cleanly hydrolyzed to **2**. This represents the first hydrolysis of an unactivated phosphate diester analogue coordinated to Co(III).

It is interesting that while the dinuclear Co(III) centers in **1**−**3** all appear to be active for cleaving phosphates with good leaving groups, the dinuclear center in **2** is the only one that provides large rate accelerations for hydrolyzing phosphates with poor leaving groups. Unlike the bridging peroxide **1** or the bridging oxide **3**, the metal hydroxide **2** can begin to deprotonate during expulsion of the leaving group which may be important for hydrolyzing phosphates with poor leaving groups.[20] Consistent with this interpretation, metal alkoxides are more reactive than metal hydroxides for cleaving phosphates with good leaving groups but the order is reversed for hydrolyzing phosphates with poorer leaving groups.[21] Metal alkoxide, metal-bridging peroxides, and metal-bridging oxides should all be able cleave phosphate diesters with poor leaving groups if the leaving group oxygen is activated by protonation or by coodination to a metal. In nature, there are dinuclear metallophosphoesterases whose active sites resemble that of **2** (fructose-1,6-biphosphatase)[22] and **3** (purple acid phosphatase).[23] Undertanding the mechanism of action of **2** and **3** in detail may give valuable insights into how a variety of dinuclear metallophosphoesterases function.

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Supporting Information Available: X-ray structural information for **1b** including crystal packing diagram, positional parameter, interatomic distances and angles and Figures S1 and S2 (13 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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